REMARKS

The Office Action dated May 17, 2007 has been received and reviewed. This response, submitted along with a Petition for a Three-Month Extension of Time, is directed to that action.

Claims 2, 17 and 27 have been amended, claim 18 has been cancelled and claim 88 is new. Support for the claim amendments and new claims can be found throughout the specification, and specifically on pages 12 and 33-46 and in Example 10. No new matter has been added.

The applicants respectfully request reconsideration based on the foregoing amendments and the following remarks.

Objections to the Specification

The Examiner objected to page 13, line 8 of the specification because the word "ursodeoxycholic acid" was misspelled. The applicants have amended the specification herein to correct the error, thus obviating the objection.

Objections to the Claims

The Examiner objected to claim 27 because the term "administered rectally" should read "is administered rectally". Claim 27 has been amended accordingly, thus obviating the objection.

Claim Rejections- 35 U.S.C. §112

The Examiner rejected claims 17 and 18 under 35 U.S.C. §112, first paragraph as not being enabled. Claim 17 has been amended herein to limit the inhibition of immune activation

to TNF-α and IL-6 production, which the applicants submit if fully enabled by the specification and examples. Furthermore, claim 18 has been cancelled. These rejections now being obviated, the applicants respectfully request that they be withdrawn.

The Examiner also rejected claims 2, 17 and 18 under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement. Regarding claim 2, the Examiner stated that the claim contained new matter that was not supported by the description. The applicants have amended claim 2 so that the claim is fully supported by the description. Furthermore, the applicants submit that the amendment to claim 17 and cancellation of claim 18 now renders the present rejections moot. Accordingly, the applicants respectfully request that the rejections be withdrawn.

Claim Rejections- 35 U.S.C. §102

The Examiner rejected claim 78 under 35 U.S.C. §102(b) as anticipated by Larghi et al. (Aliment Pharmacol Ther 11(2): 409-414, April 1997). The Examiner stated that Larghi teaches a formulation comprising "diuretics such as ursodeoxycholic acid and tauro-ursodeoxycholic acid", thus anticipating the present claim. The applicants respectfully traverse this rejection.

Claim 78 requires a pharmaceutical composition comprising ursodeoxycholic acid *and* a diuretic. Since neither ursodeoxycholic acid nor tauro-ursodeoxycholic acid is known as a diuretic, Larghi does not teach all of the limitations of the present invention. Instead, Larghi only teaches a composition comprising one element of the presently claimed invention. Accordingly, the applicants respectfully request that this rejection be withdrawn.

Claim Rejections- 35 U.S.C. §103

The Examiner rejected claims 1-2, 17-18 and 25-27 under 35 U.S.C. §103(a) as obvious over Anker et al. in view of US 5,674,855 (the '855 patent) and further in view of Gennaro et al., and claim 21 over Anker in view of the '855 patent and Gennaro and further in view of Schwartzenberg et al. The Examiner stated that it would have been obvious to one of ordinary skill in the art to administer to a human subject with chronic heart failure a thereapeutically effective amount of UDCA based on the disclosures of the prior art. The applicants respectfully traverse these rejections.

The Examiner stated that it would have been obvious to one of ordinary skill in the art to administer to a human subject with chronic heart failure a thereapeutically effective amount of UDCA based on the disclosures of the prior art. The Examiner maintains that the '855 patent teaches that UDCA is useful in treating "endotoxemia". However, the '855 patent fails to teach a definition of endotoxemia. Webster's dictionary defines "endotoxemia" as 'the presence of endotoxins in the blood'. It is not clear that the presence of *any* amount of endotoxins represents a medical condition in need of treatment, nor is there any guidance about what constitutes treatment. Thus, in the context of the '855 patent, the term "treatment of endotoxemia" is meaningless. Indeed, an approved diagnostic test for endotoxemia was not available at the time of the application, thus making any assessment for treatment unclear. Moreover, the '855 patent refers to endotoxemia only in the context of Gram-negative bacterial endotoxic shock, which is unrelated to heart failure. Accordingly, the '855 patent is relevant only for the treatment of endotoxemia in relation to endotoxic shock, and there is absolutely no suggestion that any type of treatment for heart failure-induced endotoxemia from the disclosure of the reference.

It is well known by those of ordinary skill in the art that endotoxin produces multiple biochemical effects. Such effects include:

1) Production of cytokines, including IL-1, IL-6, IL-8, tumor necrosis factor (TNF) and platelet-activating factor (PAF);

2) Activation of the complement cascade (C3a and C5a cause histamine release, and effect chemotaxis and accumulation, leading to inflammation);

3) Activation of the coagulation cascade. Initial activation of the Hageman factor can activate several humoral systems resulting in coagulation leading to thrombosis and internal bleeding, activation of the complement alternative pathway, plasmin activation leading to fibrinolysis and hemorrhaging, and kinin activation resulting in hyptension.

Ultimately, one or a combination of the foregoing effects leads to death. It is also known that not all of these biochemical effects result from similar levels of endotoxin, that multiple cells and multiple locations are involved.

Example 9 of the '855 patent is the only example where bile acids are studied, and shows only an effect on death and only with sodium cholate. There is absolutely no disclosure that any bile acids are effective on any particular end points other than death as a result of endotoxins. Furthermore, there is no suggestion in the '855 patent as to which of the many biochemical pathways listed above are affected by sodium cholate and which are not.

Moreover, the '855 patent is also silent as to whether TNF-α us even involved in endotoxin induced death (in other words, whether a reduction in TNF-α production would cause a concomitant reduction in lethality. This is particularly relevant given the very high levels of endotoxin used. Consider that Example 9 of the '855 patent uses a dose of 40 mg/kg

of LPS, which is a much higher does than the amount used for lethality studies in prior experiments (see col. 9, lines 7-8). Thus, there is a clear separation between the levels of endotoxin used in example 9 as compared to the other examples in the '855 patent. By comparison, the levels of endotoxin the present application are well below those otherswise seen (see page 38, lines 15-16 of the present application).

The applicants therefore submit that the '855 patent is not enabled for the treatment of *any* endotoxin or, contrarily, is not enabled for the treatment of endotoxemia in the context of heart failure, which involves levels of endotoxins far less than those that produce endotoxic shock. Accordingly, the skilled artisan would not be motivated to combine the teachings of the cited references to achieve the method of the present invention, and a *prima facie* case of obviousness cannot be established. The applicants respectfully request that the Examiner withdraw these rejections.

The applicants submit that the claims are now in condition for allowance, and such favorable action is respectfully requested. If any issues remain, the resolution of which can be advanced through a telephone conference, the Examiner is invited to contact the applicant's attorney at the phone number listed below.

CONDITIONAL PETITION FOR EXTENSION OF TIME

If entry and consideration of the amendments above requires an extension of time, Applicants respectfully request that this be considered a petition therefore. The Assistant Commissioner is authorized to charge any fee(s) due in this connection to Deposit Account No. 14-1263.

ADDITIONAL FEE

Please charge any insufficiency of fees, or credit any excess, to Deposit Account No. 14-1263.

Respectfully submitted,

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